IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Paul R. Schimmel

Serial No.: 08/249,689 Art Unit: 1631

Filed: May 26, 1994 Examiner: John S. Brusca

For: *"DESIGNING COMPOUNDS SPECIFICALLY INHIBITING RIBONUCLEIC ACID FUNCTION"*

Assistant Commissioner for Patents
Washington, D.C. 20231

REPLY TO EXAMINER'S ANSWER

Sir:

This is in reply to the Examiner's Answer mailed January 2, 2003. A Request for Oral Hearing accompanies this Answer along with the appropriate fee. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(5) SUMMARY OF THE INVENTION

The statement that the summary of the invention is deficient since it refers to the method as well as the resulting compounds is not understood. The invention is defined by all claims, including those that have been determined to be allowable. It is understood that only the composition claims have been rejected and are on appeal.

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(7) GROUPING OF CLAIMS

Claim 13 defines the compound of claim 11, further comprising a pharmaceutically acceptable carrier. This claim stands or falls with claim 11.

The examiner states on page 3, (2), that there was no restriction requirement between the process and product claims. The relevance of this comment is unclear. The method claims have all been determined to be allowable; the compound claims are on appeal. It would seem that this constitutes an acknowledgement that there are patentable distinctions between the method and composition claims.

(8) ARGUMENTS

Response to Examiner's Arguments

Appellant maintains that the invention is a pioneering invention - the discovery that the minor groove of RNA is the target for compounds which bind to the RNA and thereby inhibit its function. The fact that the claimed compounds have been analogized to the situation with antigens and antibodies does not detract from this position. The claimed compounds bind to RNA by virtue of their chemical structure which is complementary to the chemical structure of the target minor groove of the RNA. Antigen is also bound by antibodies by virtue of their chemical structure which is complementary to the chemical structure of the antibodies. The structure is not complementary in the sense that one strand of DNA binds to a complementary strand of DNA, but complementary in that the three dimensional structure as well as the

chemical composition is complementary to the three dimensional structure and chemical composition of the target minor groove of the RNA.

The function of the RNA is inhibited when bound by the claimed compounds. The compounds, however, are defined by their three dimensional structure and chemical composition.

With respect to the post-filing art, it was not clear that the examiner was making only a written description requirement and not combining written description with enablement. Therefore appellant submitted evidence to rebut any suggestion of lack of enablement. To the extent the examiner has made such a rejection this art should be considered.

The Legal Standard for Written Description

Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991). The purpose of the enablement requirement is to teach those of ordinary skill in the art how to make and use the invention without "undue experimentation." The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention.

The leading case for the written description requirement in the biotechnology and pharmaceutical arts is *Eli Lilly v. Univ. of Calif. Board of Regents* In *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 (herein referred to as "the '525 patent") met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

In *Enzo Biochem*, the Federal Circuit held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo II*"). The Federal Circuit held that a patentee complied with the written description requirement by depositing biological material in a public depository. The specification described the nucleotide sequence in terms of its ability to bind to *N. gonorrhoeae*. The patent had issued with no written description rejection. Nevertheless, the Federal Circuit had determined in *Enzo I* that, because the inventor had not described the actual nucleotide sequence of the probes in the patent specification, the written description was inadequate as a matter of law. In *Enzo II*, the Federal Circuit rejected its narrow interpretation of *Eli Lilly* that the disclosure of the sequence was always necessary, and instead adopted a broader interpretation of the types of disclosures that comply with the written description requirement. The court adopted provisions from the Guidelines issued by the U.S. Patent and Trademark

Office that state that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. The court found that the written description requirement was met when, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure.

This standard has been reviewed and clarified further in the recent decision of Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003). This decision was the appeal of a lengthy district court ruling on validity, infringement, and enforceability of five Amgen patents relating to production of erythropoietin (EPO), a hormone that controls formation of red blood cells. Amgen's EPO is sold under the brand name EPOGEN®. Amgen asserted that Hoechst (now Aventis Pharmaceuticals, Inc.) and Transkaryotic Therapies ("TKT") infringed U.S. Patent No. 5,547,933; 5,618,698; 5,621,080; 5,756,349; and 5,955,422, due to the filing of TKT's Investigational New Drug Application (INDA). All of the patents shared the same disclosure. TKT recombinantly produced EPO using a method that differed from the method used by Amgen and described in the patents. TKT inserted a promoter which caused the expression of ordinarily unexpressed endogenous (or "native") EPO DNA in human cells to produce the EPO.

The Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. § 112. In rendering its decision, the Court continued in the manner of *Enzo II* and applied a broad interpretation of the types of disclosures that comply with the written description requirement.

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TKT asserted that claims did not meet the written description requirement since Amgen had failed to describe the use of all mammalian and vertebrate cells, relying on the earlier *Lilly* decision.

Relying heavily on the expert testimony provided in the District Court proceeding, the Federal Circuit held that this description adequately supports the claims covering EPO made using the genus vertebrate or mammalian cells.

One question that arose out of these proceedings was whether or not Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultures vertebrate cells that produce EPO. The district court in this case found that "the specification need teach only one mode of making and using a claimed composition." *Amgen, Inc v. Hoechst Marion Roussel, Inc* 126 F.Supp.2d 69, 160, 57 USPQ 2d 1449, 1515 (D.Mass.2001).

The Specification Teaches What the Claimed Compounds Are and How to Use Them

The examiner has failed to comment in the Examiner's Answer on why the Declarations appellant has filed do not demonstrate that the specification meets the requirements under the written description requirement, based on the legal standards promulgated by the courts. The Federal Circuit in *Amgen* (Fed. Cir. 2003) makes clear that deference should be given to such expert opinion, and that the party opposing the patent must do more than merely make assertions to the contrary.

The inhibitory function of the claimed compounds cannot be obtained without a complementary structure as defined by the described chemical properties. The specification

describes the structure of the claimed compounds by illustrating the chemical properties (hydrogen bond acceptor and donor sites arranged specifically) and method of preparation (first determining the target RNA sequence and second, preparing the compounds accordingly) of the compounds. These features are present in the claims. These elements define the compounds based on the claimed interaction with a critical region in the minor groove of the target RNA. Although the compounds may be organic, inorganic, proteins, or even nucleic acids, specific binding is achieved through complementary interactions (page 38 of the specification, lines 24-31). These interactions are dependent upon hydrogen bonding (lines 29-17, bridging pages 38 and 39). Therefore, in order for the compound to bind to the target RNA, hydrogen bond donor sites, hydrogen bond acceptor sites, and chemical side groups, have to be in the correct spatial location, orientation, and have the correct charge. One of skill in the art would realize that it is this arrangement that defines the structure of the compound.

This is in fact evidenced by the declarations submitted by appellants with the last response. Declarations under 37 C.F.R. § 1.132 by Dr. Jules Rebek and Dr. James R. Williamson, respectively, were submitted with the response mailed on April 11, 2002. Both experts, neither of whom have any financial interest in this application, have stated that based on their review of the application as filed and knowledge of those skilled in the art as of that time, would have a mental picture of the structure of the chemical, or be able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.

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As discussed in the declarations under 37 C.F.R. § 1.132, the geometric configuration of the target minor groove of RNA is predicated by the presence of hydrogen bonds, the hydrophobicity of the local environment, and "the repulsive and attractive forces that exist as electrostatic entities". Each of these target RNA attributes is described in the specification. For example, the extensive stacking and base pairing of planar aromatic purines and pyrimidines inherently rendering the local environment inaccessible to solvent (or hydrophobic) is taught at page 2, lines 21-29. Furthermore, as disclosed at page 7, lines 24-26 (and again at pages 19 and 20), a network of hydrogen bonds provides not only for a stable structure within the minor groove, but also the establishment of a proper interface between compounds and their target nucleic acid (can be visualized as two pieces of a puzzle that fit together, wherein the properly spaced and oriented hydrogen bonds of the compound line the edge of one puzzle piece, and the accessible hydrogen bonds of the target RNA line the edge of the complementary piece). The maximization of these properties strengthens the electrostatic interaction between the compound and its target RNA. The end result is a specific (complementary) binding interaction that is dependent upon the defined compound structure as claimed and described.

It is well established that the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. The appellant respectfully submits that this correlation has been established.

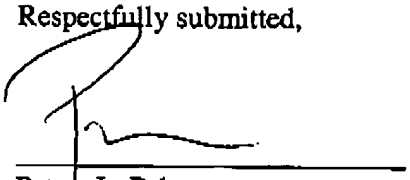
In summary, the Appellant has not only described significant structural and physical properties of the claimed compound and its cognate RNA target, Appellants have additionally

submitted two independent expert opinions that clearly support this assertion and describe the specification as being sufficient for one of ordinary skill in the art to realize the *structural* features that *define* the claimed compound. This meets the legal requirements under 35 U.S.C. 112, for written description.

(9) Summary and Conclusion

For the foregoing reasons, Appellant submits that claims 11-13, 17-19 and 21 are patentable.

Respectfully submitted,



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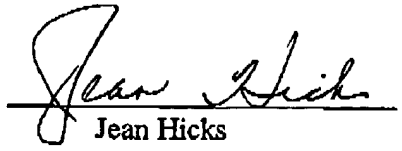

Jean Hicks

Date: March 3, 2003

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